REVIEW OF THE SYNDROMIC ASPECTS OF AIDS DEMENTIA COMPLEX AND MINOR COGNITIVE MOTOR DISORDER IN THE HAART ERA

BJ Brew

on behalf of working group 2
(Arendt G, Brew BJ, Robertson K, Sacktor N)
SYNDROMIC ASPECTS

OVERVIEW

• Epidemiology
  • Incidence/prevalence of ADC/MCMD (asymptomatics)
• Natural History
  • Survival
  • Relationship to HIV disease:
    – CD4 cell count
    – Plasma viral load
• Temporal course
SYNDROMIC ASPECTS

OVERVIEW

• Clinical Features
• Neuropsychological aspects:
  • ADC
  • Asymptomatics
• Motor Electrophysiological tests
• New Confounding-Compounding conditions
• New Risk Factors
• The way forward
SYNDROMIC ASPECTS

EPIDEMIOLOGY – AIDS DEMENTIA

• INCIDENCE:
  • Sites:
    • Australia (National data base)
    • Germany (Dusseldorf)
    • USA (Univ North Carolina and Johns Hopkins)
  • Approximately half that of the Pre HAART era

• PREVALENCE:
  • Increasing – probably (dependent on population)
INCIDENCE OF HIV DEMENTIA
Results from the Multicenter AIDS Cohort Study (MACS)

<table>
<thead>
<tr>
<th>Calendar Year</th>
<th>Incidence Rate (per 1000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>0</td>
</tr>
<tr>
<td>1991</td>
<td>10</td>
</tr>
<tr>
<td>1992</td>
<td>20</td>
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<tr>
<td>1993</td>
<td>30</td>
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<td>1994</td>
<td>40</td>
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<td>1997</td>
<td>20</td>
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<tr>
<td>1998</td>
<td>30</td>
</tr>
<tr>
<td>1999</td>
<td>40</td>
</tr>
<tr>
<td>2000</td>
<td>0</td>
</tr>
</tbody>
</table>

- Monotherapy (Mean IR=21.1)
- Dual Therapy (Mean IR=17.4)
- Triple Therapy w/PIs (Mean IR=8.5)
INCIDENCE OF HIV DEMENTIA

Johns Hopkins HIV Clinic (predominantly drug users)
PREVALENCE OF HIV DEMENTIA

Johns Hopkins HIV Clinic (predominantly drug users)
INCIDENCE/PREVALENCE ADC STAGE ≥2
(Australia – predominantly MSM)
AIDS dementia rate in Australia, 1993 - 2004, by year
SYNDROMIC ASPECTS

EPIDEMIOLOGY – MINOR COGNITIVE MOTOR DISORDER

• INCIDENCE:
  • Sites:
    • Australia (National data base)
    • Germany (Dusseldorf)
    • USA (Univ North Carolina and Johns Hopkins)
  • ?increasing

• PREVALENCE:
  • ?increasing (but prevalence of neuropsychological deficits in asymptomatic patients is unchanged)
Prevalence of Neuropsychological impairment in asymptomatic patients

Criterion 1 (2 SD in 1 test/1 SD in 2 tests; 32% in controls)
Criterion 2 (2 SD in 2 tests; 6% in controls).

Cysique et al JNV 2004
SYNDROMIC ASPECTS

EPIDEMIOLOGY – MINOR COGNITIVE MOTOR DISORDER

• Three explanations:
  • Flow from the cognitively normal to asymptomatic but neuropsychologically impaired and flow of these to MCMD
  • Shift of demented population to MCMD
  • Combination of both – bidirectional shift
SYNDROMIC ASPECTS

ADC: EPIDEMIOLOGY III

• NATURAL HISTORY
  • Pre HAART:
    • Mean time to death for ADC patients in general was six months
  • Post HAART:
    • Mean time to death is 48+ months
Survival post ADC diagnosis by CD4 cell count

SYNDROMIC ASPECTS

ADC: EPIDEMIOLOGY II

• RELATIONSHIP TO HIV DISEASE:
  • Presence and severity:
    • CD4 cell count
      – pre-HAART: mean = 50-100
      – HAART:
        – CD4 cell count now higher at ADC diagnosis:
<table>
<thead>
<tr>
<th>Study</th>
<th>1990-1995 Mean CD4 cell count/mm³ at diagnosis ADC</th>
<th>1996-1998 Mean CD4 cell count/mm³ at diagnosis ADC</th>
<th>1999-2001 Mean CD4 cell count/mm³ at diagnosis ADC</th>
<th>2001-2003 Mean CD4 cell count/mm³ at diagnosis ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACS</td>
<td>150</td>
<td>286</td>
<td>518</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Sacktor et al 2001)</td>
<td>(Sacktor, Personal communication)</td>
<td></td>
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<tr>
<td>AUS</td>
<td>70</td>
<td>160</td>
<td></td>
<td>418</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Dore et al 1999)</td>
<td></td>
<td>(Cysique et al 2004)</td>
</tr>
</tbody>
</table>
SYNDROMIC ASPECTS

ADC: EPIDEMIOLOGY II

• RELATIONSHIP TO HIV DISEASE:
  • Presence and severity:
    • Plasma viral load
      – pre-HAART: weak relationship
      – HAART:
        – No correlation at baseline (NEAD cohort, Sevigny et al 2004) (Cysique et al 2004)
        – Neuropsych impairment may occur with VL<50 (Cysique et al 2005 unpublished)
SYNDROMIC ASPECTS

Asymptomatic patients with plasma VL<50 with altered neuropsychological performance over 27 months

<table>
<thead>
<tr>
<th>Change in composite RCI*</th>
<th>Session 2 (6 months) (N=81)</th>
<th>Session 3 (15 months) (N=51)</th>
<th>Session 4 (27 months) (N=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>36% (5/14)**</td>
<td>43% (3/7)</td>
<td>64% (9/14)</td>
</tr>
<tr>
<td>Non-decliners stable</td>
<td>50% (21/42)</td>
<td>43% (13/30)</td>
<td>59% (13/22)</td>
</tr>
<tr>
<td>decliners</td>
<td>36% (9/25)</td>
<td>43% (6/14)</td>
<td>100% (2/2)</td>
</tr>
</tbody>
</table>

*RCI: reliable change index
**% = no. with VL<50/total number with any VL

Cysique et al 2005 unpublished
Prevalence of Global Neuropsychological Impairment by Education in European and African Centers: WHO Neuropsychiatric Study

<table>
<thead>
<tr>
<th></th>
<th>Munich, Germany</th>
<th>Kinshasa, Zaire</th>
<th>Nairobi, Kenya</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A/HIV+</td>
<td>S/HIV+</td>
<td>A/HIV+</td>
</tr>
<tr>
<td>Low-education subjects, % impaired</td>
<td>11.8</td>
<td>31.0*</td>
<td>25.0*</td>
</tr>
<tr>
<td>High-education subjects, % impaired</td>
<td>4.0</td>
<td>22.2*</td>
<td>2.8</td>
</tr>
<tr>
<td>Total sample, % impaired</td>
<td>7.1</td>
<td>25.7*</td>
<td>9.6</td>
</tr>
</tbody>
</table>

A- asymptomatic, S-symptomatic
*Significant intracenter differences, asymptomatic or symptomatic HIV+ vs. HIV- subjects: P < 0.05

Maj et al. Arch Gen Psych. 1994:51-61
Frequency of Dementia in Academic Alliance Cohort-Uganda (n= 81)

- MSK 0 (no impairment): 31%
- MSK 0.5 (equivocal/subclinical impairment): 23%
- MSK 1.0 (mild dementia): 46%

Wong et al, Neurology 2004 62;S5:A444.
Variable course:
- stable clinically for months-years
- progress but very slowly
- improve – variable rate
SYNDROMIC ASPECTS

ADC Natural History – Temporal aspects

• Temporal Classification
  • Active:
    • Progressive (aka subacute or chronic active)
    • Stable: fixed deficits with virological/immunological abnormalities – ADC in “equilibrium” (aka chronic inactive)
    • Regressive: deficits are improving
    • Fluctuating
  
• Inactive: fixed neurological deficits with no virological/immunological abnormalities (aka chronic inactive)

SYNDROMIC ASPECTS

ADC Natural History – Temporal aspects

Temporal Classification

• **Difficulties:**
  - Real time identification of activity:
    - CSF HIV RNA to 10 cpml or less?
      - Abacavir ADC data
    - CSF ceramide/sphingomyelin
ADC and HAART

Real time identification of Inactive ADC

?CSFVL<10cpml

Cysique et al JAIDS 2005
CSF Ceramide is Elevated in Active Dementia

Ceramide

HIV + ND
HIV + ID
HIV + AD

C16 C18 C22 C24

# = p < 0.05
* = p < 0.05
** = p < 0.01
*** p < 0.001

Sacktor et al. J Neuroimmunol 2004
CSF HNE is Elevated in Active HIV Dementia Cases

4-HNE Adducts

- HIV+ ND
- HIV+ ID
- HIV+ AD

# = p < 0.05          * = p < 0.05          ** = p < 0.01
*** p < 0.001

Sacktor et al. J Neuroimmunol 2004
CSF Sphingomyelin is Elevated in Inactive HIV Dementia Cases

Sacktor et al. J Neuroimmunol 2004
CSF from Active HIV Dementia Cases Shows Increased Mitochondrial Toxins

Mitochondrial potential (% of control)

HIV+ no dementia  Inactive HIV dementia

Sacktor et al. J Neuroimmunol 2004
SYNDROMIC ASPECTS

• Markers of ADC activity and inactivity:
  • Accuracy of CSF HIV RNA 10 cpml and below
  • Robust for each ADC stage:
    • Ceramide levels in the brain decrease with severe ADC
      ? What happens to the CSF

• Robust for duration of inactivity:
  • ?Sphingomyelin increase in CSF remains even in patients with prolonged inactive ADC
SYNDROMIC ASPECTS

ADC: CLINICAL PHENOTYPE

• Still the same core categories of abnormalities in cognitive, motor and behavioral performance – *at the moment*

• ?same weighting in each:
  • Are the behavioral deficits as common or severe?

• Less severe in general - Clinical staging (*Tozzi et al J Nvirol 2004; Sevigny et al Neurology 2005*)
SYNDROMIC ASPECTS

ADC: NEUROPSYCHOLOGICAL ASPECTS

• Less severe disease:
  • Neuropsychological impairment:
    • Global- mild impairment / moderate impairment (of each ADC cohort):
      Pre HAART 10.3% / 89.7% vs HAART 44.4% / 59.6% (p=.02)
    • Specific areas: learning, memory and complex attention/psychomotor speed still impaired but less deficit in motor-coordination and semantic fluency
  • But pattern change in asymptomatics premonitory of change in ADC???

Cysique et al 2005 unpublished
SYNDROMIC ASPECTS

NEUROPSYCHOLOGICAL DEFICITS IN ADC

Cysique et al 2005 unpublished
SYNDROMIC ASPECTS

NEUROPSYCHOLOGICAL DEFICITS IN ASYMPTOMATIC PATIENTS

Cysique et al JNV 2004
SYNDROMIC ASPECTS

MOTOR TESTS (Arendt)

*Three tests of motor function
*Contraction and RAM combined more reliable
*sensitivity/specificity: 80/90%
*HAART has led to a decrease in severity of abnormalities
*motor tests correlate with neuropsychological tests but to varying extents
Electrophysiological Test Results according to the Duesseldorf Classification

**Abbreviations:**
- *Sustained:* electrophysiology abnormal despite HAART
- *Transient(1) pathological:* transient improvement after initiation of HAART
- *Transient(0) pathological:* improvement after HAART then deterioration then improvement after HAART correction
- *Incipient(1) pathological:* beginning deterioration of pathological electrophysiological results
- *Incipient(0) pathological:* beginning deterioration of electrophysiological results with normalisation after initiation of HAART
Electrophysiological Test Results according to Dementia Activity

Abbreviations:
*Subacute progressive dementia*: untreated, severe progressive dementia
*Chronic active dementia*: treated, incomplete virological control, slowly progressive dementia
*Chronic inactive dementia*: treated, complete virological control, recovery from neurological deficits and stable
SYNDROMIC ASPECTS

Electrophysiological Test Results by severity (no HAART benefit)
SYNDROMIC ASPECTS

Electrophysiological Test Results by severity (transient HAART improvement)
Electrophysiological Test Results by severity
(transient improvement after correction of HAART failure)
SYNDROMIC ASPECTS

Electrophysiological Test Results by severity (improvement post HAART)
SYNDROMIC ASPECTS

Electrophysiological Test Results by severity
SYNDROMIC ASPECTS

Electrophysiological Test Results by severity
(incomplete virological control)

chronically active

Year

%
SYNDROMIC ASPECTS

Electrophysiological Test Results by severity (complete virological control)

chronically inactive

[Bar chart showing percentage of severe, moderate, and mild cases from 1998 to 2004]
SYNDROMOMIC ASPECTS

Electrophysiological Test Results by severity
Correlation between Contraction time and Grooved Pegboard

\[ r(CT;GPT) = 0.338 \]
Correlation between Contraction time and digit-span

$r(CT; DST) = -0.244$
SYNDROMIC ASPECTS

Correlation between Contraction time and trail-making test 1

$r(CT;TMT_1) = 0.480$
Correlation between Contraction time and trail-making test 2

\[ r(\text{CT};\text{TMT2}) = 0.296 \]
SYNDROMIC ASPECTS

NEW CONFOUNDING-COMPOUNDING FACTORS

• Which?
  • Increasing Age
    • Accounted for 30% of deficit in complex attention/psychomotor speed
    • 44.83 ± 8.97yrs cf pre HAART age 37.17 ± 8.29 (Cysique et al 2005)
  • Hepatitis C (Cherner et al Neurology 2005;64(8):1343-7)
SYNDROMIC ASPECTS
NEW CONFOUNDING-COMPOUNDING FACTORS

• Which? (cont’d)
  • Alzheimer’s disease: risk factors:
    • Increased age
    • Increased cholesterol (especially at mid-life)
    • Amyloid excess:
      • Autopsy data (Stanley et al JNEN 1994; Esiri et al JNNP 1998; Green et al AIDS 2005)
      • Increased APP (Nebuloni et al AIDS 2001), increased APP breakdown (Liao et al JBC 2004) and inhibition of amyloid fragment catabolism (Rempel and Pulliam AIDS 2005)
SYNDROMIC ASPECTS
NEW CONFOUNDING-COMPOUNDING FACTORS

• Which? (cont’d)
  • Alzheimer’s disease (cont’d):
    • Tau deposition *(Stanley et al JNEN 1994;*
    • Pathology shift to hippocampus *(Anthony JNV et al 2004; Anthony JNV et al 2004)*
    • CSF amyloid/p-tau *(Brew et al 2005)*
SYNDROMIC ASPECTS

NEW CONFOUNDING-COMPOUNDING FACTORS

• Which? (cont’d)
  • Vascular dementia:
    • Increased carotid artery intimal thickness
    • Cerebrovascular disease risk factors (SMART data set n=2945):
      43.3% smoke
      8.9% diabetic
      23.4% are hypertensive requiring medication
      25.1% have hypercholesterolaemia requiring medication
      1.7% prior stroke
  • How to identify extent of contribution?
    • Mere presence is probably insufficient
NEW RISK FACTORS

• Increasing Age
  • Hawaii data
    \textit{(Valcour et al Neurology 2004;63(5):822-7)}
• Nadir CD4 cell count
  • Correlates with verbal recall \textit{(Cysique et al 2005)}
  • ?not with global neuropsychological score
  • ?=surrogate for disease duration
• Depression
• Diabetes/glucose intolerance
\textit{(Valcour et al JAIDS 2005;38(1):31-6.)}

• Duration of HIV disease?
Neurocognitive Classification of Older and Younger HIV+ Cohorts - Hawaii Cohort

* P < 0.001

• Older HIV+ individuals were more likely to have either MC/MD or HIV-D compared to younger HIV+ individuals.

(Valcour et al Neurology 2004;63:822-827)
SYNDROMIC ASPECTS

The Way Forward:

The CHARTER Study

The SMART Neurology substudy
SMART Study Design

Participants with CD4 > 350

n = 3000

Virologic Suppression (VS) Strategy
[Use ART to maintain viral load as low as possible throughout follow-up]

n = 3000

Drug Conservation (DC) Strategy
[Stop or defer ART until CD4 < 250; then episodic ART based on CD4 cell count to increase counts to > 350]

Follow-up for 6-9 years
SMART
Baseline Characteristics (N=2707)
(As of 15 January 2005)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.5</td>
</tr>
<tr>
<td>Female</td>
<td>26 %</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>African American or</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>38 %</td>
</tr>
<tr>
<td>Latino or Hispanic</td>
<td>16 %</td>
</tr>
<tr>
<td>White</td>
<td>47 %</td>
</tr>
<tr>
<td>Other</td>
<td>3 %</td>
</tr>
</tbody>
</table>
SMART Baseline ART History

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent ART naïve</td>
<td>5 %</td>
</tr>
<tr>
<td>Time since first prescribed AR therapy</td>
<td>6</td>
</tr>
<tr>
<td>(median (in years))</td>
<td>[3; 8]</td>
</tr>
<tr>
<td>Time since known to be HIV positive</td>
<td>8</td>
</tr>
<tr>
<td>(median (in years))</td>
<td>[5; 12]</td>
</tr>
</tbody>
</table>
CD4+ (cells/mm$^3$), mean 657
Median, [25$^{th}$; 75$^{th}$] 590 [460; 790]
SMART Baseline CD4+ Nadir

Mean 277
Median [25th ; 75th] 262 [155 ; 380]
HIV RNA

- $\leq 50$: 33%
- $\leq 400$: 61%
- 401 - 1,000: 6%
- 1,001 - 5,000: 11%
- 5,001 - 10,000: 4%
- 10,001+: 17%

**Highest log HIV RNA observed**

$log$ copies/mL

- Median: 4.7
- $[25^{th}; 75^{th}]$: [4.0; 5.2]
### Hypotheses for Viral Suppression Arm

<table>
<thead>
<tr>
<th>Peripheral Neuropathy</th>
<th>Neurocognitive Functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increased incidence</td>
<td>• Preserved, or improved neurocognitive function</td>
</tr>
<tr>
<td>• Increased symptom severity in patients with extant peripheral neuropathy</td>
<td></td>
</tr>
</tbody>
</table>
Rationale for SMART Neurology Substudy

Hypotheses for Drug Conservation Arm

<table>
<thead>
<tr>
<th>Peripheral Neuropathy</th>
<th>Neurocognitive Functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased incidence</td>
<td>• Decline in neurocognitive function</td>
</tr>
<tr>
<td>• Decreased symptom severity in patients with extant peripheral neuropathy</td>
<td></td>
</tr>
</tbody>
</table>
### Primary Objectives

<table>
<thead>
<tr>
<th>Peripheral Neuropathy</th>
<th>Neurocognitive Functioning</th>
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<tbody>
<tr>
<td><em>To compare the DC group with the VS group for</em></td>
<td></td>
</tr>
<tr>
<td>• Development of peripheral neuropathy</td>
<td></td>
</tr>
<tr>
<td>• Changes in peripheral neuropathy symptoms in patients with neuropathy at baseline</td>
<td></td>
</tr>
<tr>
<td><em>To compare the DC group with the VS group for</em></td>
<td></td>
</tr>
<tr>
<td>• Changes in neurocognitive functioning</td>
<td></td>
</tr>
</tbody>
</table>
Secondary and Tertiary Objectives

- To compare the DC group with the VS group for:
  - Incidence of neurocognitive impairment
  - Incidence of HIV AIDS Dementia Complex
  - Resolution of peripheral neuropathy, in the subset of patients with peripheral neuropathy at baseline.
- Baseline characteristics
  - Influence on outcome primary endpoints
Measures of Neurocognitive Functioning

• Depression screen (CES-D) *(10 minutes)*
• Alcohol & Drug questionnaire *(5 minutes)*
• Neuropsychological Test Battery *(25-30 minutes)*
  • Grooved Pegboard
  • Timed Gait
  • Finger Tapping
  • Color Trails A and B

⇒ *Quantitative Neurological Performance Z-Score (QNPZ-5)*
Endpoints and Sample Sizes

- **Endpoint 1**: To compare DC and VS groups for change in neurocognitive function
  - To detect a difference of 0.27 in mean change in the QNPZ-5 scores from baseline to the average of years 1 through 5

=> *Sample size required*
- n=600 patients

*Price et al, Neurol 1999*
Endpoints and Sample Sizes

• **Endpoint 2: To compare DC and VS groups for development of PN**
  - DC 8% versus VS 15%
  - DC 20% versus VS 30%

=> *Sample size required*
  - n=800 patients without PN at baseline
Endpoints and Sample Sizes

- Endpoint 3: To compare DC and VS groups for change in PN symptoms in patients with PN at baseline

=> Sample size required

- n=approximately 120 patients with PN at baseline
920 patients co-enrolled in the SMART Study

800 patients without peripheral neuropathy at baseline

120 patients with symptomatic peripheral neuropathy at baseline

Randomization into the SMART Study

DC Group

VS Group

920 patients participate in the peripheral neuropathy component of the study

At selected sites all patients will participate in neurocognitive component of the study n=600
SMART Neurology Substudy Protocol Team

Edwina Wright, M.B.B.S., F.R.A.C.P. Chair
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Philip Andrew, R.N., B.S.
Bruce Brew, M.B.B.S., M.D., F.R.A.C.P.
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Ellis Wood, Community Representative

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Kevin Robertson, Ph.D.
Ronald Tikofsky, Ph.D.
SUMMARY AND RECOMMENDATIONS

• Epidemiology:
  • Incidence halved/prevalence doubled but MCMD increase – if so from which population?
  • Survival much longer
  • CD4 cell count much higher
  • Plasma VL not correlated
  • Temporal profile changed
  • Concept of active stable?
  • Time for inactivity
  • Markers
SYNDROMIC ASPECTS

SUMMARY AND RECOMMENDATIONS

- Clinical phenotype:
  - unchanged categories– behavioural component?
  - Less severe
  - Older
- Neuropsychology: ?pattern change
- Motor electrophysiological tests
- New confounds: age, hepatitis C, vascular risk factors, AD
- New risk factors: age, nadir CD4?, depression, glucose intolerance?
- Further studies:
  - SMART
  - CHARTER